Remarks/Arguments

Claims 1-17 are pending in the application and claims 1-2, 6-8 and 13 are rejected under 35 USC 103.

Claims 1-2, 6-8 and 13 are rejected under 35 USC 103(a) as obvious over US Patent 6,653,306 to Alexander et al. in view of the article to Brater et al. (Kidney International, 1984, Vol. 26, pp. 183-189).

Alexander teaches in column 4, lines 26-33 that a combination therapy comprising a therapeutically effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist is useful to treat circulatory disorders, including cardiovascular disorders such as hypertension, congestive heart failure, cirrhosis and ascites and in column 5 lines 10-13 that another combination therapy of interest would consist essentially of three active agents, namely, an AII antagonist, an aldosterone receptor antagonist agent and a diuretic. However, Alexander fails to teach applicants' claimed combination of the aldosterone receptor antagonist eplerenone, the diuretic bumetanide and the angiotensin receptor blocker valsartan.

Brater et al. teach that bumetanide is a new loop diuretic which is 40-50 times as potent as furosemide. However, Brater also teach on page 187, that "Assessing the time at which peak urinary excretion rate of the drug occurred revealed negligible differences between bumetanide and furosemide at the doses used in this study. Consequently, in terms of time course of absorption, the two diuretics appear little different, exhibiting a similarity which is consistent with data from normal subjects taken in our laboratory."

Such teachings in Brater would not motivate one skilled in the art to add the bumetanide of Brater et al. into the composition of Alexander since, even the enhanced potency of bumetanide of 40-50 times still provided no improvement in the the peak urinary excretion rate for bumetanide compared to furosemide. Further, no conclusions of the efficacy for bumetanide compared to furosemide can be drawn, since on page 188, Brater et al. states that "With oral dosing, the additional factor of a changed time course of delivery may also contribute, but its importance in quantitative terms cannot be discerned from our data. Future paired studies in the same patient, delivering the same total amount of drug into the urine by the intravenous compared to the oral route of administration will be needed to dissect the relative contributions of these determinants of response."

Therefore, a *prima facie* case for obviousness has not been established and withdrawal of this ground of rejection under 35 USC 103 is respectfully requested.

Respectfully submitted,

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Date: August 28, 2009